HFA-305
Dockets Management
Branch
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Approval Date:_____

# FREEDOM OF INFORMATION SUMMARY

# ORIGINAL NEW ANIMAL DRUG APPLICATION

# NADA 141-172

## Ractopamine hydrochloride (PAYLEAN®) plus Tylosin phosphate (TYLAN®)

1) **For increased weight gain, improved feed efficiency and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein from 150 lb (68kg) to 240 lb (109 kg) body weight, and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis.***
2) **For improved feed efficiency and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein from 150 lb (68kg) to 240 lb (109 kg) body weight, and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis.***

**Sponsored by:**

**Elanco Animal Health**
**A Division of Eli Lilly and Company**
**Lilly Corporate Center**
**Indianapolis, Indiana 46285**

NADA 141-172

FOIS 1

# FREEDOM OF INFORMATION SUMMARY

Combined use of PAYLEAN® and TYLAN ® in Finishing swine

## I. GENERAL INFORMATION:

**NADA:** 141-172

**Sponsor:** Elanco Animal Health
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

**Generic Names:** Ractopamine hydrochloride
Tylosin phosphate

**Trade Names:** PAYLEAN®
TYLAN®

**Marketing Status:** OTC

## II. INDICATIONS FOR USE:

1) For increased weight gain, improved feed efficiency and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein from 150 lb (68kg) to 240 lb (109 kg) body weight, and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis.*
2) For improved feed efficiency and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein from 150 lb (68kg) to 240 lb (109 kg) body weight, and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis.*

## III. DOSAGE:

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles, ractopamine hydrochloride as per 21 CFR 558.500(d)(1)(i) and tylosin phosphate as per 21 CFR 558.625(f)(1)(vi)(e). Ractopamine hydrochloride is supplied as a Type A medicated article in a concentration of 9 grams ractopamine hydrochloride activity per pound. Tylosin phosphate is supplied as a Type A medicated article in concentrations of 10, 40, or 100 grams tylosin phosphate activity per pound.

| | | |
|---|---|---|
| B. | Route of Administration: | Oral, *via* the feed. |
| C. | Recommended Dosage: | |
| | Ractopamine hydrochloride | 1) Ractopamine hydrochloride is added to finishing swine feed at concentrations of 1) 4.5 g/ton (5 ppm) for increased rate of weight gain, improved feed efficiency and increased carcass leanness, and 2) 4.5 to 18 g/ton (5 ppm to 20 ppm) for improved feed efficiency and increased carcass leanness. Both levels are fed in a complete ration containing at least 16% crude protein from 150 lb (68kg) to 240 lb (109 kg) body weight. |
| | Tylosin phosphate | Tylosin phosphate is added to finishing swine feed at a concentration of 100 g/ton for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*. |

**CAUTION:** For finishing swine only. Feed as sole ration for 21 days between 150 lb (68 kg) and 240 lb (109 kg) body weight. Not for use in breeding swine.

## IV. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population, or 3) where the combination contains more than one nontopical antibacterial active ingredient/animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Ractopamine hydrochloride, as provided by Elanco Animal Health, has previously been separately approved for use in finishing pigs for increased rate of weight gain and improved feed efficiency and increased carcass leanness (21 CFR 558.500(d)(1)(i)). Tylosin phosphate as provided by Elanco Animal Health, has previously been separately approved for use in finishing pigs for the prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(e)). Effectiveness for each drug, ractopamine hydrochloride and tylosin phosphate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 140-863 and 12-491, respectively.

Because ractopamine hydrochloride and tylosin phosphate each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that ractopamine hydrochloride plus tylosin phosphate provide appropriate concurrent use for the intended target population. The use of ractopamine hydrochloride plus tylosin phosphate provides appropriate concurrent use because these drugs are intended to treat different conditions (ractopamine hydrochloride, weight gain, feed efficiency or carcass leanness; tylosin phosphate, ileitis associated with *Lawsonia intracellularis*) likely to occur simultaneously with sufficient frequency in finishing swine. There is no more than one nontopical antibacterial (tylosin phosphate) contained in this combination animal drug intended for use in Type C medicated feed. Ractopamine hydrochloride is not considered to be an antibacterial animal drug for such use in swine for the purposes of Section 512(d)(4) of the FFDCA.

## V. ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination, or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such a combination active ingredient or animal drug is safe for the target animal.

Ractopamine hydrochloride, as provided by Elanco Animal Health, has previously been separately approved for use in finishing pigs for increased rate of weight gain, improved feed efficiency and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein for 150 lb (68 kg) to 240 lb (109 kg) body weight (21 CFR 558.500(d)(1)(i)). Tylosin phosphate, as provided by Elanco Animal Health, has previously been separately approved for use in finishing pigs for the prevention and/or control of porcine

proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis* (21 CFR 558.625(f)(1)(vi)(e)). Target animal safety for each drug, ractopamine hydrochloride and tylosin phosphate, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in approved NADAs 140-863 and 12-491, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of ractopamine hydrochloride or tylosin phosphate when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety study is required for approval of NADA 141-172.

## VI. HUMAN SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal for the respective active ingredients or animal drugs in the combination exceeds the established tolerance, or one or more active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or drug in the combination.

### A. Toxicity Studies

Safety of the individual drugs in this combination product has been established by data in NADA 140-863 for ractopamine hydrochloride, and NADA 12-491 for tylosin phosphate.

### B. Safe Concentration of Total Residues

For ractopamine hydrochloride, a tolerance is established for residues of ractopamine hydrochloride parent in edible swine tissues of 0.05 ppm in muscle, and 0.15 ppm in liver as codified under 21 CFR 556.570.

For Tylosin phosphate, a tolerance of 0.2 ppm is established for negligible residue of tylosin in uncooked fat, muscle, liver, and kidney in swine as codified under 21 CFR 556.740.

## C. Residue Non-Interference Study

### C.1. Tissue Residue Non-Interference Study in Swine with Ractopamine and Tylosin. T4V629503.

Investigator: D. Hughes, A. Sharp and J. Turk
Covance Laboratory
3301 Kinsman Boulevard
Madison, Wisconsin 53704

This study was conducted to determine non-interference in the tissue depletion in swine of the ractopamine and tylosin combination. The swine were fed *ad libitum* a combination of ractopamine (20 ppm) and tylosin (100 g/ton) for ten days. The animals were euthanized and tissues collected at practical zero withdrawal (12 hours). Liver tissue was collected from animals in both treatment groups.

Livers from the ractopamine treatment were assayed by high performance liquid chromatography with fluorescence detection. Liver was assayed for tylosin bioactive residues in liver by microbiological methods. Liver tissues fortified with ractopamine and tylosin was stored at –20°C+ 10°C for 28 days and 16 days, respectively, before the appropriate assays were performed. The storage conditions well exceed the approved stability for liver tissue fortified with ractopamine and tylosin.

The ractopamine residues in the liver at practical zero-time withdrawal were 0.013 ppm, which is below the tolerance established for swine liver at 0.15 ppm. Tylosin residues in the liver at practical zero-time withdrawal were below the limit of quantitation of the method of 0.05 ppm and therefore, below the tolerance established for swine liver at 0.2 ppm.

The results indicate that the residue profile of ractopamine and tylosin are not altered when the drugs are fed in combination at the levels tested in this study.

### C.2. Storage Stability and Assay Non-Interference

To demonstrate storage stability, two control liver samples were spiked with either 149 or 150 ppb of ractopamine and analyzed on day zero and after 28 days of freezer storage, a period of time that exceeds the 14 days incurred samples were held before analysis. Similarly, two control liver samples were spiked with 0.2 ppm of tylosin and analyzed on day zero and after 16 days of freezer storage, a period of time that exceeds the 14 days incurred samples were held before analysis. Observed recoveries showed no significant differences over the storage period.

To show assay noninterference, two control samples were spiked with either 150 ppb ractopamine or 0.2 ppm tylosin, while another three were fortified with 150 ppb ractopamine and 0.2 ppm tylosin. The control sample spiked only with tylosin was analyzed for ractopamine and nothing was detected; the same result was obtained when the control sample spiked only with ractopamine was analyzed for tylosin. When two of the samples spiked with both drugs were analyzed for tylosin and when the one remaining sample containing both drugs was assayed for ractopamine adequate recoveries were obtained.

**D. Withdrawal Time**

There is a 0 day withdrawal for ractopamine hydrochloride and tylosin phosphate. Refer to the approved NADAs 140-863, and 12-491, respectively. Tissue residue non-interference was adequately shown; therefore the combination qualifies for a zero withdrawal.

**E. Regulatory Method**

Refer to the approved NADAs for ractopamine hydrochloride and tylosin phosphate for the approved regulatory methods in NADA 140-863 and 12-491 respectively.

**F. User Safety Concern**

Refer to Material Safety Data Sheets (MSDS) for these NADAs for ractopamine hydrochloride and tylosin phosphate (NADA 140-863 and 12-491 respectively) by contacting the manufacturer for the MSDS.

## VII. AGENCY CONCLUSIONS:

The data submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that use of ractopamine hydrochloride at a concentration of 4.5 to 18 g/ton (5 ppm to 20 ppm) plus tylosin phosphate (100 g/ton) with a zero withdrawal period is safe and effective for the claims indicated in section II of this FOI Summary.

Pursuant to 21 CFR 514.106(b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

Attached labeling: Type C Medicated Feed (Blue Bird) –Finishing pigs

Net Weight lb (kg) on bag or bulk

# Paylean®/Tylan® Finishing Swine Feed

## Type C Medicated Feed

For increased rate of weight gain, improved feed efficiency, and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein from 150 lb (68 kg) to 240 lb (109 kg) body weight, and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis.*

### Active Drug Ingredients

| | |
|---|---|
| Ractopamine hydrochloride | 4.5 g/ton |
| Tylosin phosphate | 100 g/ton |

### Guaranteed Analysis

| | |
|---|---|
| Crude Protein, not less than | 16.00 % |
| Lysine, not less than | _____% |
| Crude Fat, not less than | _____% |
| Crude Fiber, not more than | _____% |
| Calcium, not less than | _____% |
| Calcium, not more than | _____% |
| Phosphorus, not less than | _____% |
| Salt[1], not less than | _____% |
| Salt[1], not more than | _____% |
| Sodium[2], not less than | _____% |
| Sodium[2], not more than | _____% |
| Selenium, not less than | _____ppm |
| Zinc, not less than | _____ppm |

[1]If added.

[2]Shall be guaranteed only when total sodium exceeds that furnished by the maximum salt guarantee.

### Ingredients

Each ingredient must be named in accordance with the names and definitions adopted by the Association of American Feed Control Officials.

### Directions for Use

Feed continuously as the sole ration for 21 days between 150 lb (68 kg) to 240 lb (109 kg) body weight.

**WARNING:** The active ingredient in Paylean, ractopamine hydrochloride, is a beta-adrenergic agonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for use in humans. Keep out of the reach of children. The Paylean formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling Paylean, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse eyes thoroughly with water. If irritation persists, seek medical attention. The material safety data sheet contains more detailed occupational safety information. To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

**CAUTION:** Not for use in breeding swine.

**MANUFACTURED BY**

BLUE BIRD FEED MILL
Anytown, USA 12345

Net Weight lb (kg) on bag or bulk

# Paylean®/Tylan® Finishing Swine Feed

## Type C Medicated Feed

For improved feed efficiency and increased carcass leanness in finishing swine fed a complete ration containing at least 16% crude protein from 150 lb (68 kg) to 240 lb (109 kg) body weight, and for prevention and/or control of porcine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*.

### Active Drug Ingredients

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|---|---|
| Ractopamine hydrochloride | 4.5 to 18 g/ton |
| Tylosin phosphate | 100 g/ton |

### Guaranteed Analysis

| | |
|---|---|
| Crude Protein, not less than | 16.00 % |
| Lysine, not less than | _____ % |
| Crude Fat, not less than | _____ % |
| Crude Fiber, not more than | _____ % |
| Calcium, not less than | _____ % |
| Calcium, not more than | _____ % |
| Phosphorus, not less than | _____ % |
| Salt[1], not less than | _____ % |
| Salt[1], not more than | _____ % |
| Sodium[2], not less than | _____ % |
| Sodium[2], not more than | _____ % |
| Selenium, not less than | _____ ppm |
| Zinc, not less than | _____ ppm |

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